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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/557,299	11/18/2005	Qiang Guo Chen	100998-1P US	9259

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/557,299	CHEN ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-18 and 20* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response to the restriction requirement filed August 24, 2007 is acknowledged. In the response, claims 1, 7, 11, and 17 were amended, and claims 9 and 19 were canceled.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-8, 10-18, 20, and SEQ ID NO: 1 in the reply filed on August 24, 2007 is acknowledged. The traversal is on the ground(s) that the claims as amended share a special technical feature linking them over the prior art. Applicant's arguments were found persuasive, because the prior art of Sivaraja *et al.* does not anticipate the claims as amended. Also, Applicant's amendment to claims 7 and 17 obviated the need to elect a specific SEQ ID NO: for examination. Therefore, all of the pending claims will be examined on the merits.

Priority

3. Applicant's benefit claim under 35 U.S.C. 119(e) to Provisional Applications 60/473,054 and 60/472,967, both filed on May 23, 2003, is acknowledged.

Information Disclosure Statement

4. Applicant's submission of an Information Disclosure Statement on February 3, 2006 is acknowledged. A signed copy is enclosed.

Drawings

5. The drawings filed on November 18, 2005 are acceptable.

Claim Objections

6. Claim 5 is objected to because of the following informalities: This claim appears to contain a typographical error. It appears that the words "DNA primase" were omitted after "*S. aureus*."

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-18, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 10-18, and 20 are indefinite, because independent claims 1 and 11 recite the limitation "the triphosphates" in line 4 and line 5, respectively. There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for "the ribonucleoside triphosphates."

Claims 6 and 16 contain the trademark/trade names SYBR® Green II, RiboGreen®, and YO-PRO®-1. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35

U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe nucleic acid binding dyes and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-6, 8, 10-16, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sivaraja *et al.* (US 6,043,038; cited previously) in view of Jones *et al.* (Analytical Biochemistry (1998) 265: 368-374).

These claims are drawn to fluorescence-based methods of assaying DNA primase activity and also screening test compounds for their ability to modulate DNA primase activity.

Regarding claims 1 and 11, Sivaraja *et al.* teach a method for identifying compounds that modulate DNA primase activity comprising:

(a) providing a reaction mix comprising a nucleic acid template, a DNA primase, ribonucleoside triphosphates, and a test compound (column 2, lines 53-60 or column 24, line 48 – column 26, line 2)

(b) incubating the reaction mix such that the ribonucleoside triphosphates polymerize to form RNA (column 2, lines 60-63 or column 26, line 3)

(c) detecting the RNA product, wherein a change in the observed signal in the presence of the test compound compared to the signal observed in the absence of the test compound indicates that test compound modulates DNA primase activity (column 2, line 63 – column 3, line 2 or column 26, lines 4-17).

Regarding claims 4, 5, 14, and 15, Sivaraja *et al.* teach that the DNA primase is *E. coli* DNA primase, *S. aureus* DNA primase, *S. pneumoniae* DNA primase, or *H. influenzae* DNA primase (column 6, lines 25-54).

Regarding claims 8 and 18, Sivaraja *et al.* teach that the assay is conducted in the presence of helicase (column 6, lines 25-28 and column 24, lines 48-56).

Sivaraja *et al.* do not teach that the RNA product is detected using a fluorescent marker that binds thereto as required by claims 1 and 11. Sivaraja *et al.* teach also do not teach that the detection step requires no further steps of separating the RNA product from the reaction mix as required by claims 1 and 11.

Jones *et al.* teach fluorescence-based methods of quantifying RNA (see abstract). Jones *et al.* teach that the RiboGreen reagent is a fluorescent dye that binds RNA in solution with high sensitivity (see abstract and pages 369-371). Regarding claims 6, 10, 16, and 20, Jones *et al.* teach detecting RNA by measuring the increase in fluorescence intensity of the RiboGreen dye in response to RNA binding (page 369, column 2). Jones *et al.* further teach that quantification of RNA using the RiboGreen reagent is amenable to high throughput automation (page 374).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to detect RNA products produced by the method of Sivaraja *et al.* using the RiboGreen reagent taught by Jones *et al.* An ordinary artisan would have been motivated to do so since Jones *et al.* taught that RiboGreen was capable of directly detecting RNA in a biochemical reaction mixture with high sensitivity (see pages 369-374 cited above). An ordinary artisan would have had a reasonable expectation of success in directly detecting RNA products generated in the primase assay of Sivaraja *et al.* without performing further RNA separation steps, since Jones *et al.* taught that the RiboGreen reagent could detect RNA in the presence of salts, detergents, proteins, and organic solvents (see pages 372-374 and Table 1). Finally, regarding claims 2, 3, 12, and 13, it would have been obvious for an ordinary artisan to add the RiboGreen reagent taught by Jones *et al.* either before or after the polymerization step taught by Sivaraja *et al.*, since section 2144.04 IV C of the MPEP states, "Selection of any order of mixing

ingredients is *prima facie* obvious." Here, there is no particular reason for the RiboGreen reagent to be added before or after the polymerization step, and therefore, its addition at either time is *prima facie* obvious in the absence of secondary considerations. Thus, the methods of claims 1-6, 8, 10-16, 18, and 20 are *prima facie* obvious in view of the combined teachings of Sivaraja *et al.* and Jones *et al.* in the absence of secondary considerations.

10. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sivaraja *et al.* (US 6,043,038; cited previously) in view of Jones *et al.* (Analytical Biochemistry (1998) 265: 368-374) and further in view of Khopde *et al.* (Biochemistry (2002) 41: 14820-14830) and further in view of Sheaff *et al.* (Biochemistry (1993) 32: 3027-3037) and further in view of Tseng *et al.* (The Journal of Biological Chemistry (1982) 257(13): 7280-7283).

The combined teachings of Sivaraja *et al.* and Jones *et al.* result in the methods of claims 1-6, 8, 10-16, 18, and 20, as discussed above.

These references do not teach that the nucleic acid template used in the method comprises $d(CT)_{30}GCAAAGC$ (SEQ ID NO: 1) as required by claims 7 and 17.

Khopde *et al.* studied the affinity and sequence specificity of *E. coli* DNA primase (see abstract and pages 14820-14821). Khopde *et al.* teach that the trinucleotide CTG is required for *E. coli* DNA primase activity (pages 14820 & 14824), and further teach using an oligonucleotide comprising the sequence d(CTGCAAAGC) as a template for DNA primase (Table 1 and pages 14821-14824 – the G4ori-wt sequence). Khopde *et al.* state, "[T]he DNA binding affinity of primase depends on the length of the template, and it was optimal above 20 bp (page 14825)." Khopde *et al.* also teach that the CTGCAA sequence is semi-conserved, and its inclusion in

DNA template increased the binding affinity of the primase (page 14825, page 14828, and Table 1). Khopde *et al.* concluded that the binding of DNA primase to a template nucleic acid is length and sequence dependent (page 14828).

Khopde *et al.* do not teach the that the template comprising d(CTGCAAAGC) further comprises $d(CT)_{17}$ immediately 5' of the d(CTGCAAAGC) sequence.

Sheaff *et al.* (Biochemistry (1993) 32: 3027-3037) studied the mechanism by which calf thymus DNA primase binds to a DNA template and synthesizes a complementary RNA molecule (see abstract). In these studies, Sheaff *et al.* used an oligonucleotide comprising $d(CT)_{17}$ as a template for DNA primase (see Tables I, II, and IV and pages 3028-3029, where the $d(TC)_{30}$ template is taught). Sheaff *et al.* teach that upon binding of DNA primase to a DNA template, polymerization of the first two ribonucleotides occurs very slowly followed by rapid polymerization of additional nucleotides (see abstract and page 3027). Sheaff *et al.* teach that the binding of DNA primase is length dependent with a higher affinity for longer templates (pages 3030 and 3033). Sheaff et al. also teach that the processivity of DNA primase is composition dependent, since templates having a higher GC-content appear to increase the stability of the primase-template-nascent RNA primer complex, thereby increasing the processivity of the primase (pages 3034-3035).

Sheaff *et al.* teach that $d(TC)_{30}$, poly(dT), poly(dTdC), $d(TCC)_{20}$, and $d(ACT)_{20}$ are useful as templates for DNA primase (page 3030), but do not teach using a poly(dCdT) template.

Tseng *et al.* characterized the DNA primase activity isolated from human lymphocytes (see abstract and page 7280). Tseng *et al.* teach that poly(dIdT), poly(dCdT), and poly(dT) are useful templates for monitoring DNA primase activity (page 7283).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize a template nucleic acid comprising SEQ ID NO: 1 in the method resulting from the combined teachings of Sivaraja *et al.* and Jones *et al.* An ordinary artisan would have been motivated to utilize a template nucleic acid comprising d(CTGCAAAGC) since Khopde *et al.* taught that the CTG trinucleotide was required for *E. coli* DNA primase activity (pages 14820 & 14824), and a template comprising the CTGCAAAGC sequence showed a higher affinity for DNA primase than a homopolymeric template (page 14825, page 14828, and Table 1). An ordinary artisan also would have been motivated by the teachings of Khopde *et al.* and Sheaff *et al.* to increase the length of the template to greater than 20 bp, since both references taught that DNA primase bound more tightly to longer templates (see page 14825 of Khopde *et al.* and pages 3030 and 3033 of Sheaff *et al.*). Furthermore, since Sheaff *et al.* taught that increasing the GC-content of the template increased the processivity of DNA primase (pages 3034-3035), an ordinary artisan would have been motivated to increase the length of the d(CTGCAAAGC) template by adding a sequence such as the poly(dCdT) sequence taught by Tseng *et al.* to the 5' terminus. Addition of the poly(dCdT) sequence taught by Tseng *et al.* to the 5' end of the d(CTGCAAAGC) template taught by Khopde *et al.* results in a template comprising the instant SEQ ID NO: 1. Regarding the choice of the poly(dCdT) sequence, an ordinary artisan would have recognized that this sequence was an equivalent useful for achieving the same purpose, namely increasing DNA primase processivity. As noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents useful for the same purpose. Also, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose.

Finally, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In this case, all of the elements of the claimed template sequence were known in the art at the time of invention as evidenced by the teachings of Khopde *et al.*, Sheaff *et al.*, and Tseng *et al.* An ordinary artisan could have combined these elements using known oligonucleotide synthesis methods without producing a change in their respective functions. In other words, the combination of the DNA primase template elements taught by Khopde *et al.*, Sheaff *et al.*, and Tseng *et al.* would produce a template for DNA primase. This template would be expected to function in the method resulting from the teachings of Sivaraja *et al.* and Jones *et al.* in a predictable and potentially improved manner. Therefore, the use of a template comprising SEQ ID NO: 1 is prima facie obvious over the cited references in the absence of secondary considerations.

Conclusion

11. No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kozlowski et al. (US 6,096,499) teaches a multi-step method for screening

compounds for their effect on DNA primase activity based on monitoring the incorporation of radioactive nucleotides (see Example 2, column 25, line 35 – column 26, line 17).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Art Unit 1637
November 9, 2007

/Cynthia Wilder/
Patent Examiner
Art Unit 1637

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